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ORIGINAL RESEARCH

Primary Prophylaxis for High-Risk Varices in Patients with Hepatocellular Carcinoma and Portal Vein Tumor Thrombus Delayed Hepatic Decompensation: A Retrospective, Propensity Score Matching Study

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Background and Aims: The prevalence of clinically significant portal hypertension (CSPH) is high in patients with hepatocellular carcinoma (HCC) and portal vein tumor thrombus (PVTT). There was no evidence of whether primary prophylaxis is beneficial in reducing hepatic decompensation in these patients.

Methods: Clinical records of 445 patients with pathology or radiology-confirmed HCC and PVTT from January 2013 to December 2022 were reviewed, 142 patients having concurrent high-risk varices (HRV) without hepatic decompensation were enrolled. Patients were divided into the prophylaxis group and non-prophylaxis group. Propensity score matching was used for group comparison. The primary endpoint was decompensation-free survival (DFS), and the secondary endpoints were the incidence of esophageal variceal bleeding (EVB) and overall survival (OS).

Results: The incidence of EVB was higher in the non-prophylaxis group than in the prophylaxis group (46.8% VS 21%, p = 0.001). DFS was longer in the prophylaxis group than in the non-prophylaxis group (84 days vs 66 days, p = 0.009). There was no difference in OS between two groups. In multivariate analysis, primary prophylaxis was associated with longer DFS (HR 0.806, p = 0.017); Immunotherapy (IO) was associated with longer DFS and OS; Barcelona Clinic Liver Cancer (BCLC) stage D was associated with shorter DFS and OS.

Conclusion: Primary prophylaxis delays hepatic decompensation in HCC patients with PVTT. The incidence of EVB was also lower in the prophylaxis group, particularly in those treated with NSBB. First-line IO treatment is independently associated with better DFS and OS.

Keywords: clinically significant portal hypertension, hepatocellular carcinoma, portal vein tumor thrombus, hepatic decompensation

Introduction

Hepatocellular carcinoma (HCC) is globally the third most deadly cancer, having age-standardized incidence and mortality rates of 8.6 and 7.4 per 100,000 person-years, respectively, in 2022.[1] Projections foresee a 55.0% and 56.4% surge in these rates by 2040.[2] A considerable portion of HCC patients also suffer from cirrhosis,[3] and a vast number of these individuals manifest clinically significant portal hypertension (CSPH), defined as a hepatic venous portal gradient (HVPG) of 10 mmHg or more. Complications stemming from CSPH include the formation of ascites and variceal

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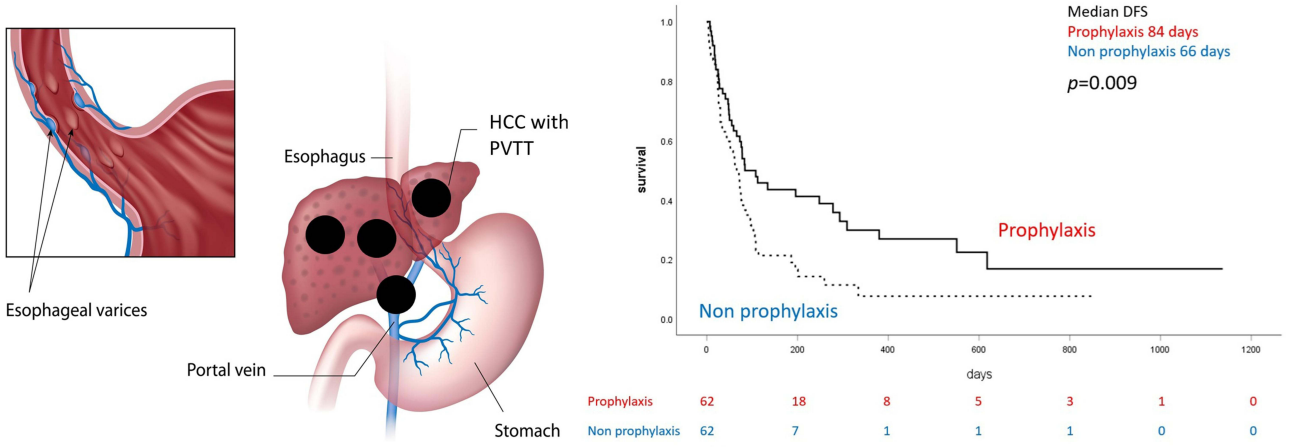
Graphical Abstract



bleeding. Earlier studies revealed that 48.5% of HCC patients exhibit esophagogastric varices,[4] and among these patients, 27.7% have high-risk varices (HRV).[5]

Despite the considerable prevalence of HRV in HCC patients, specific guidance for primary or secondary prevention of variceal bleeding in this population is missing. A recent guideline from the American Association for the Study of Liver Diseases recommends prescribing non-selective beta-blockers (NSBB) to patients with CSPH, in the absence of contraindications.[6] This advice aligns with the Baveno VII consensus recommendation[7] but was primarily aimed at patients without HCC. With most studies excluding patients with HCC, treatment strategies for CSPH in this group of patients lack clinical evidence.

In patients with HCC and CSPH, tumor invasion into the portal vein is associated to worse outcomes. The incidence of portal vein tumor thrombosis (PVTT) varies from 16% to 36% across different regions and literature.[8,9] Many studies have determined a correlation between PVTT and increased instances of esophageal variceal bleeding (EVB) or diminished survival rates in patients with HCC and HRV.[10–12] When EVB occurs in patients at the Barcelona Clinic Liver Cancer (BCLC) C stage, mortality and rebleeding rates are extraordinarily high, especially in those with main portal vein thrombosis.[13]

A previous prospective study suggested that consistent endoscopic variceal ligation (EVL) until eradication lowers the rate of recurrent bleeding in patients with relatively preserved liver function of Child-Turcotte-Pugh's A and B.[14] However, PVTT was associated with an increased risk of recurrent bleeding. A retrospective study pointed to a survival benefit of primary EVL in patients with HRV who underwent trans-arterial chemoembolization (TACE),[15] and it also showed a correlation between PVTT and shorter variceal bleeding-free survival and overall survival (OS). A recent randomized controlled trial (RCT) indicated fewer EVB and better OS with EVL than NSBB for primary prophylaxis in early-stage HCC (BCLC A/B) patients with HRV.[16] Synthesizing these studies, the results suggest that either primary or secondary prophylaxis of EVB improves the outcome of HCC patients with HRV, specifically, in patients with early-stage HCC. However, it is yet to be determined whether the clinical benefit could extend to BCLC C/D stage patients.

Recently, systemic treatment for advanced HCC has significantly improved, leading to increased survival, even in patients with PVTT.[17] The regimen evolved from tyrosine kinase inhibitor (TKI) only to immunotherapy (IO) with anti-programmed death-1 (anti-PD-1) and anti-programmed death ligand-1 (anti-PD-L1).[18] The IMbrave 150 study[19] demonstrated that patients with Vp4 invasion, who received atezolizumab and bevacizumab, achieved a median OS of up to 7.6 months. With the benefits of NSBB in preventing hepatic decompensation in patients with CSPH confirmed by the PREDESCI study,[20] the primary prophylaxis goal for patients with CSPH has shifted from preventing EVB to preventing hepatic decompensation, according to the Baveno VII consensus.[7]

While no studies have examined the effects of primary prophylaxis of hepatic decompensation in HCC patients with PVTT and CSPH, these survivals have been improved by existing systemic therapy. If hepatic decompensation can be prevented or delayed, the survival of these groups of patients would be further improved. This study seeks to illuminate the feasibility and clinical benefits of primary prophylaxis, focusing on hepatic decompensation and EVB, among HCC patients with PVTT and HRV.

Materials and Methods

Patients

Four hundred and forty-five patients with pathology or radiology-confirmed HCC and PVTT who received esophagogastroduodenoscopy (EGD) within 3 months of their HCC diagnosis, and did not undergo liver transplantation or surgery, were enrolled from January 2013 to December 2022. Of these patients, 172 (38.7%) had no EV, 103 (23.1%) had low-risk EV, and 170 (38.2%) had HRV. Of the 170 patients with HRV, 28 presented with hepatic decompensation and were excluded, leaving 142 patients who entered the final analysis (Figure 1). Within the scope of the 142 patients, 19 participated in our previous RCT.[16] In line with the principles of portal hypertension treatment, the patients who received NSBB as a primary prophylaxis of EVB were prescribed 10 mg of propranolol twice per day, with dose adjustments made until the heart rate reached 55 bpm or 75% of its baseline, as recommended. The patients who underwent EVL as primary prophylaxis of EVB were subsequently followed every month for ligation until the varices were eradicated. An EGD would then be performed in the subsequent 3 months, follow by once after 6 months, as recommended. If no recurrence of EV was observed, EGD would be scheduled annually. Clinical characteristics, such as hepatitis B and C virus infection statuses, BCLC stage, Child Turcotte Pugh (CTP) class, the Model of End-stage Liver Disease Sodium Score (MELD-Na), and the Albumin-Bilirubin (ALBI) grade were recorded. Tumor size, number, the presence of metastasis, treatment details, and all relevant laboratory data including complete blood count, renal, hepatic, coagulation

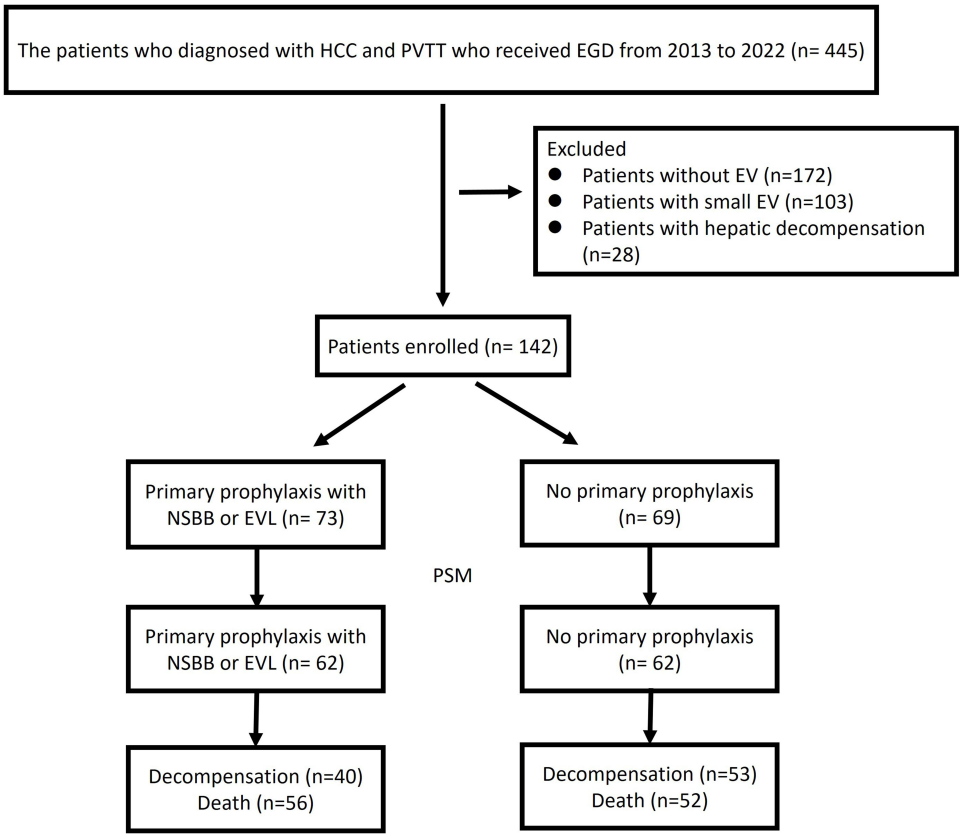


Figure 1 Study flowchart.

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function, and serum level of albumin were also recorded. The treatment modalities such as TACE, TKI, and IO were also recorded. The main regimens of IO were anti-PD-1, with nivolumab and pembrolizumab, only 1 patient received Atezolizumab and Bevacizumab.

The study was carried out in compliance with the Declaration of Helsinki and received approval from the Institutional Review Board of Taipei Veterans General Hospital (VGHIRB No. 2023–11-005CC). Consent waivers were procured for the retrospective study, and patient information along with their records were rendered anonymous and de-identified before being analyzed.

PVTT and Hepatic Decompensation

The diagnosis of PVTT was established on dynamic computer tomography (CT) or magnetic resonance (MR) findings, identifiable as a filling defect that partially or completely obstructed the vessels in the portal venous phase and demonstrated enhancement during the arterial phase. vP4 was defined as PVTT located at the main trunk of the portal vein. If the CT image could not distinguish the PVTT and blend thrombus, further MRI study would be arranged. There were 25% (31/124) patients receiving MRI in our study.

The presence of EV was assessed by EGD and classified as F1, small and straight varices; F2, moderately sized, tortuous varices; and F3, large, tumorous varices. The size of EV from F2 and F3, or F1 with red coloring, was defined as HRV.[21]

According to Baveno VII,[7] hepatic decompensation is defined as overt ascites, overt hepatic encephalopathy (West Haven grade > 2), or variceal bleeding (an endoscopic finding with active bleeding, white nipple sign, or large varices without other potential bleeders). When the patient experiences more than one type of hepatic decompensation, the first event will be recorded. If the patients expire within 6 weeks after variceal bleeding, the cause of death is recorded as variceal bleeding. Other causes of death include hepatic failure/tumor progression or infection.

Statistical Analysis

The primary endpoint was decompensation-free survival (DFS), calculated from the date of HCC diagnosis to the date of hepatic decompensation, the patient's last visit, or December 31, 2022. In patients prescribed EVL or NSBB for primary prophylaxis, DFS calculation started from the date of first prescription or procedure up to the first hepatic decompensation episode, the patient's last visit, or December 31, 2022. The secondary endpoint was OS, calculated from the HCC diagnosis date to the patient's death, last visit, or December 31, 2022. For patients receiving EVL or NSBB as primary prophylaxis, OS calculation started from either the NSBB prescription date or the first EVL procedure.

Comparative analysis of categorical variables was performed using Fisher's exact test or a $\chi 2$-test with Yates' correction, and continuous variables through the Mann–Whitney *U*-test with statistical significance ($P < 0.05$) or near significance ($P < 0.1$) were subjected to multivariate analysis using a forward stepwise logistic regression model. A P-value less than 0.05 was considered statistically significant for hazard ratio (HR). Propensity score matching analysis was performed using a one-to-one nearest-neighbor matching method, considering variables such as ALBI grade, CTP class, alpha fetal protein (AFP), MELD-Na, treatment modality, and BCLC stage. IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY, USA) was used for all statistical analysis. All authors accessed the study data and approved the final manuscript for review.

Results

Baseline Clinical Characteristics and Outcomes

All 142 patients were classified as BCLC C/D HCC and had HRV without hepatic decompensation at the time of HCC diagnosis. Among them, 69 patients (48.6%) did not receive any prophylactic treatment for HRV, while 73 (51.4%) did receive prophylactic treatment (EVL for 32 patients (22.5%) and NSBB for 41 patients (28.9%)) (Figure 1). After propensity score matching, each group (prophylaxis versus non-prophylaxis) contained 62 matched patients. Hepatic decompensation developed in 93 patients (75%), and 108 patients (87.1%) expired during a median follow-up period of 109 days.

Compared to patients receiving primary prophylaxis of EVB, those without prophylaxis had similar baseline clinical characteristics and treatment of HCC (Table 1). DFS was longer in the prophylaxis group than in the non-prophylaxis group (84 days vs 66 days, $p = 0.009$) (Figure 2a). Incidences of EVB were higher in the non-prophylaxis group than in the prophylaxis group (46.8% vs 21%, $p = 0.001$) (Table 2). The percentage of patients who died due to EVB was similar in both groups (11.3% vs 8.1%, $p = 0.601$). There was no significant difference in OS (Figure 2b).

In the prophylaxis group, each group had 29 matched patients (NSBB vs EVL). Patients treated with NSBB or EVL exhibited similar clinical characteristics and received similar HCC treatments (Supplementary Table 1). There was no difference in DFS between the NSBB and the EVL groups (Figure 3a). However, the incidence of EVB was higher in the

Table 1 Baseline Characteristics

Patient Demographic	All (N = 124)	Primary Prevention (N = 62)	No Prevention (N = 62)	p value
Age (years)	**61 (53–69)**	**60 (53–69)**	**63 (54–69)**	***0.644***
Sex (M/F) (%)	100/24 (80.6%/19.4%)	49/13 (79%/21%)	51/11 (82.2%/17.8%)	0.649
HBsAg (±) (%)	73/51 (58.9%/41.1%)	36/26 (58.1%/41.9%)	37/25 (59.7%/40.3%)	0.820
Anti-HCV (±) (%)	23/101 (18.5%/81.5%)	9/53 (14.5%/85.5%)	14/48 (22.6%/77.4%)	0.248
Alcoholism (±) (%)	33/89 (27%/73%)	18/43 (29.5%/70.5%)	15/46 (24.6%/75.4%)	0.541
CTP class (A/B/C) (%)	45/71/8 (36.3%/57.3%/6.4%)	23/36/3 (37.1%/58.1%/4.8%)	22/35/5 (35.5%/56.4%/8.1%)	0.765
Median follow-up times (days)	109 (58–238)	92 (58–347)	113 (56–176)	0.697
Biochemistry				
Albumin (g/dl)	3.4 (2.9–3.7)	3.4 (2.9–3.6)	3.4 (2.9–3.7)	0.685
ALT (U/L)	53 (34–82)	52 (33–80)	58 (35–84)	0.456
AST (U/L)	93 (55–144)	98 (54–160)	90 (65–135)	0.726
ALKP (U/L)	179 (121–279)	185 (124–318)	172 (119–262)	0.354
T-Bil (mg/dl)	1.74 (1.07–2.84)	1.74 (1.05–2.77)	1.72 (1.11–3.08)	0.791
Creatinine (mg/dl)	0.83 (0.70–1.00)	0.82 (0.70–0.95)	0.89 (0.71–1.06)	0.265
PT INR	1.19 (1.12–1.32)	1.19 (1.13–1.30)	1.22 (1.11–1.34)	0.532
PLT (X1000mm^3)	162 (118–216)	173 (135–220)	142 (112–217)	0.175
MELD-Na score	14.02 (10.84–19.64)	13.92 (10.73–19.88)	14.18 (11.04–19.38)	0.782
ALBI score	−1.87 (−2.24~−1.34)	−1.87 (−2.17~−1.35)	−1.90 (−2.27~−1.34)	0.576
Tumor Factors				
Tumor > 10cm (Y/N)	31/93 (25%/75%)	15/47 (24.2%/75.8%)	16/46 (25.8%/74.2%)	0.836
Tumor number	4 (1–4)	4 (1–4)	4 (1–4)	0.732
AFP (ng/mL)	1032 (24–14,974)	802 (19–16,418)	1460 (95–11,019)	0.547
Metastasis (Y/N) (%)	39/85 (31.5%/68.5%)	19/43 (30.6%/69.4%)	20/42 (32.3%/67.7%)	0.847
vP4 (Y/N) (%)	83/41 (66.9%/33.1%)	42/20 (67.7%/32.3%)	41/21 (66.1%/33.9%)	0.849
BCLC stage (C/D) (%)	95/29 (76.6%/23.4%)	49/13 (79%/21%)	46/16 (74.2%/25.8%)	0.524
TKI (Y/N) (%)	72/52 (58.1%/41.9%)	36/26 (58.1%/41.9%)	36/26 (58.1%/41.9%)	1.000
IO (Y/N) (%)	19/105 (15.3%/84.7%)	10/52 (16.1%/83.9%)	9/53 (14.5%/85.5%)	0.803
TACE (Y/N) (%)	8/116 (6.5%/93.5%)	4/58 (6.5%/93.5%)	4/58 (6.5%/93.5%)	1.000
RT (Y/N) (%)	20/104 (16.1%/83.9%)	10/52 (16.1%/83.9%)	10/52 (16.1%/83.9%)	1.000

Note: Continuous variables are expressed as the median with the 25th and 75th percentiles.

Abbreviations: AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; ALK-P, alkaline phosphatase; ALT, alanine aminotransferase; BCLC, the Barcelona Clinic Liver Cancer; CTP, Child-Turcotte-Pugh; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; IO, immunotherapy; MELD, Model For End-Stage Liver Disease; PT-INR, prothrombin time international normalized ratio; RT, radiotherapy; TACE, transarterial chemoembolization; TKI, tyrosine kinase inhibitor.

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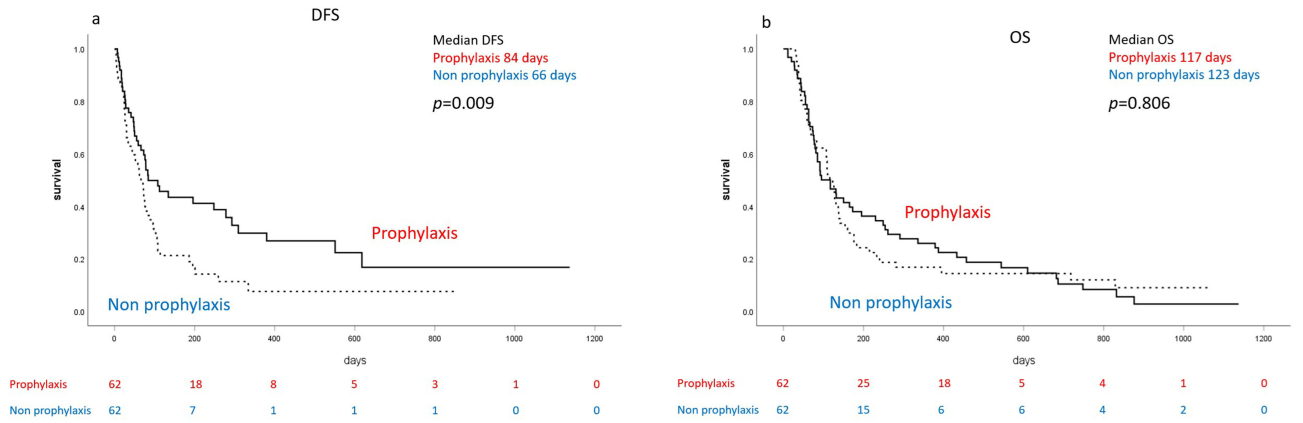

Figure 2 (**a**) Decompensation free survival between prophylaxis group and non-prophylaxis group. (**b**) Overall survival between prophylaxis group and non-prophylaxis group.

EVL group than in the NSBB group (31% vs 10.3%, $p = 0.028$) (Table 2). No meaningful difference in OS between the NSBB and the EVL groups (Figure 3b).

Subgroup analysis (Table 3) revealed that the incidence of EVB was higher in the non-prophylaxis group in patients with CTP class A (63.6% vs 12.5%, $p < 0.001$) but not in patients with CTP class B and C. DFS was longer in the prophylaxis group in patients with CTP class B and C (84 days vs 58 days, $p = 0.022$). In patients with BCLC stage C, higher incidence of EVB was noted in the non-prophylaxis group and longer DFS was noted in the prophylaxis group, with no difference in OS; But in patients with BCLC stage D, there were no differences in incidence of EVB, DFS, and OS. In patients receiving IO as treatment modality, DFS and OS were longer than the main group but there were no differences in incidence of EVB, DFS, and OS between the prophylaxis and non-prophylaxis group. In patients receiving TKI, the incidence of EVB was higher in the non-prophylaxis group (20% vs 48.6%, $p = 0.012$), but there was no difference in DFS and OS. DFS was shortest in patients experienced EVB, but there was no difference in OS between different types of hepatic decompensation (Supplementary Table 2).

Factors Associated with Hepatic Decompensation and OS

The multivariate analysis revealed that primary prophylaxis (HR 0.601, $p = 0.017$) and IO (HR 0.486, $p = 0.037$) correlated with extended DFS, whereas BCLC D was linked with diminished DFS (HR 3.129, $p < 0.001$) (Table 4). With respect to OS, the multivariate analysis showed that IO (HR 0.437, $p = 0.017$) correlated with improved OS. On the contrary, MELD-Na score > 20 (HR 2.016, $p = 0.006$), AFP > 400 ng/mL (HR 1.810, $p = 0.006$), and BCLC stage D (HR 6.415, $p < 0.001$) were associated with a worse OS (Supplementary Table 3).

Table 2 Outcomes

Outcomes	All (124)	Prophylaxis (62)	Non-Prophylaxis (62)	*p*	NSBB (29)	EVL (29)	*p*
EVB (Y/N) (%)	42/82 (33.9%/66.1%)	13/49 (21%/79%)	29/33 (46.8%/53.2%)	**0.001**	3/26 (10.3%/89.7%)	9/29 (31%/69%)	**0.028**
Decompensation type Ascites/HE/EVB (%)	41/10/42 (33.1%/8.1%/33.9%)	21/6/13 (33.9%/9.7%/21%)	20/4/29 (32.2%/6.5%/46.8%)	0.091	14/4/3 (48.3%/13.8%/10.3%)	6/3/9 (20.7%/10.3%/31%)	**0.046**
DFS (days)	76 (27–136)	84 (28–249)	66 (26–108)	**0.009**	78 (67–90)	112 (70–155)	0.467
PD (Y/N) (%)	97/27 (78.2%/21.8%)	47/15 (75.8%/24.2%)	50/12 (80.6%/19.4%)	0.514	7/22 (24.1%/75.9%)	8/21 (27.6%/72.4%)	0.764
Cause of death LF or PD/EVB/infection (%)	89/12/6 (71.8%/9.7%/4.8%)	46/5/4 (74.2%/8.1%/6.5%)	43/7/2 (69.4%/11.3%/3.2%)	0.601	24/2/1 (82.8%/6.9%/3.4%)	20/3/2 (69%/10.3%/6.9%)	0.663
OS (days)	117 (59–238)	117 (58–302)	123 (59–178)	0.806	91 (69–113)	150 (82–219)	0.093

Note: The p value with significance was labeled as bold font.
Abbreviations: DFS, decompensation free survival; EVB, esophageal variceal bleeding; HE, hepatic encephalopathy; LF, liver failure; OS, overall survival; PD, progressive disease.

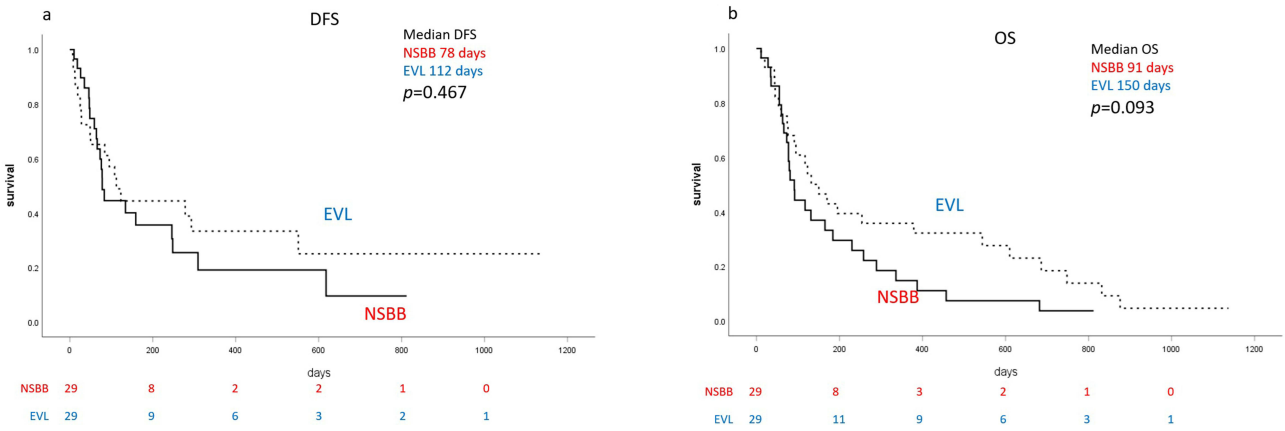

Figure 3 (**a**) Decompensation free survival between EVL group and NSBB group. (**b**) Overall survival between EVL group and NSBB group.

In the prophylaxis group, IO was associated with improved DFS (HR 0.370, p = 0.029) according to univariable analysis. However, multivariate analysis indicated that BCLC stage D was the only factor associated with diminished DFS (HR 3.626, p = 0.002) (Supplementary Table 4). Moreover, IO (HR 0.418, p = 0.025) correlated with improved OS

Table 3 Subgroup Analysis of Outcomes

Outcome	All	Prophylaxis	Non-Prophylaxis	*P*
CTP class A	**46**	**24**	**22**	
EVB (Y/N) (%)	17/29 (36.9%/63.1%)	3/21 (12.5%/77.5%)	14/8 (63.6%/36.4%)	*<0.001*
DFS (days)	83 (44–278)	108 (48–309)	76 (29–259)	0.233
OS (days)	141 (85–457)	117 (74–457)	160 (127–718)	0.315
CTP class B/C	**78**	**38**	**40**	
EVB (Y/N) (%)	25/53 (32.1%/67.9%)	10/28 (26.3%/73.7%)	15/25 (37.5%/62.5%)	*0.290*
DFS (days)	71 (26–195)	84 (28–551)	58 (24–103)	0.022
OS (days)	95 (45–230)	91 (53–261)	107 (43–137)	0.252
BCLC stage C	**95**	**49**	**46**	
EVB (Y/N) (%)	30/65 (31.6%/68.4%)	8/41 (16.3%/83.7%)	22/24 (47.8%/52.2%)	*0.001*
DFS (days)	96 (50–334)	196 (50–618)	76 (44–186)	0.023
OS (days)	141 (83–395)	173 (74–457)	138 (109–281)	0.950
BCLC stage D	**29**	**13**	**16**	
EVB (Y/N) (%)	12/17 (41.4%/58.6%)	5/8 (38.5%/61.5%)	7/9 (43.8%/56.2%)	*0.774*
DFS (days)	26 (12–66)	26 (13–73)	26 (5–30)	0.487
OS (days)	52 (35–79)	26 (27–79)	43 (38–69)	0.594
IO	**19**	**10**	**9**	
EVB (Y/N) (%)	5/14 (26.3%/73.7%)	3/7 (30%/70%)	2/7 (22.2%/77.8%)	*0.701*
DFS (days)	293 (28-)	331 (28-)	114 (51-)	0.552
OS (days)	554 (76–876)	682 (85–876)	395 (76-)	0.670
TKI	**70**	**35**	**35**	
EVB (Y/N) (%)	24/46 (34.3%/65.7%)	7/28 (20%/80%)	17/18 (48.6%/51.4%)	*0.012*
DFS (days)	86 (48–334)	112 (55–618)	77 (44–201)	0.087
OS (days)	139 (81–457)	195 (66–640)	137 (109–281)	0.667

Note: Continuous variables are expressed as the median with the 25th and 75th percentiles.
Abbreviations: BCLC, the Barcelona Clinic Liver Cancer; CTP, Child-Turcotte-Pugh; DFS, decompensation free survivals; EVB, esophageal variceal bleeding; OS, overall survivals; IO, immunotherapy; TKI, tyrosine kinase inhibitor.

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Table 4 Multivariate Analysis of Decompensation Free Survival Between Prophylaxis Group and Non-Prophylaxis Group

Variable	N	Univariate Analysis		Multivariate Analysis	
		Hazard Ratio (95% CI)	*p*	Hazard Ratio (95% CI)	*p*
Age (y/o) > 65/≦ 65	44/78	0.850 (0.562–1.287)	0.443		
Gender M/F	100/24	1.001 (0.599–1.674)	0.997		
HBsAg Y/N	73/51	0.946 (0.630–1.420)	0.789		
Anti-HCV Y/N	23/101	0.936 (0.553–1.584)	0.806		
Alcoholism Y/N	33/89	1.456 (0.927–2.288)	0.103		
ALBI grade 3/1+2	35/89	1.408 (0.900–2.202)	0.134		
MELD-Na > 20/≦20	29/95	1.320 (0.809–2.154)	0.266		
ALKP(U/L) >200/≦200	45/59	0.975 (0.617–1.542)	0.913		
Platelet (mL^{-1}) > 100K/≦100K	106/18	0.644 (0.379–1.094)	0.103		
Tumor > 10cm Y/N	31/93	0.734 (0.451–1.196)	0.215		
AFP (ng/mL) > 400/≦400	69/55	1.351 (0.899–2.029)	0.148		
Metastasis Y/N	39/85	1.005 (0.654–1.544)	0.981		
vP4 invasion Y/N	83/41	1.201 (0.784–1.842)	0.400		
TKI Y/N	72/52	0.500 (0.328–0.763)	0.001		
IO Y/N	19/105	0.452 (0.236–0.865)	0.017	0.486 (0.247–0.956)	0.037
TACE Y/N	8/116	0.946 (0.436–2.050)	0.888		
RT Y/N	20/104	0.889 (0.520–1.522)	0.669		
BCLC D/C	29/95	3.618 (2.242–5.838)	<0.001	3.129 (1.926–5.084)	<0.001
Prophylaxis Y/N	62/62	0.620 (0.412–0.932)	0.005	0.601 (0.397–0.912)	0.017

Abbreviations: AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; ALK-P, alkaline phosphatase; BCLC, the Barcelona Clinic Liver Cancer; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; IO, immunotherapy; MELD, Model For End-Stage Liver Disease; PT-INR, prothrombin time international normalized ratio; RT, radiotherapy; TACE, transarterial chemoembolization; TKI, tyrosine kinase inhibitor.

in univariable analysis, yet BCLC stage D (HR 4.290, $p < 0.001$) remained as the only factor associated with deteriorated OS in the multivariable analysis (Supplementary Table 5).

Discussion

This is the first study to investigate the benefits of primary prophylaxis of hepatic decompensation specifically targeted at HCC patients with PVTT and HRV. The study unveiled several crucial findings. First, the primary prophylaxis using NSBB or EVL linked to an extended DFS, but not OS, in HCC patients with PVTT and HRV. Second, there were no differences in decompensation or OS between the NSBB or EVL groups, although the frequency of EVB was notably higher in the EVL group. Finally, patients subjected to IO displayed more favorable results in terms of DFS and OS for HCC patients with PVTT and HRV.

The approach for primary and secondary prevention of EVB in HCC patients has been used following the principles for cirrhotic patients in recent guidelines.[20,22] However, the prognosis for HCC patients with portal hypertension is notably worse than for cirrhotic patients due to the complexities of HCC treatment and rapidly declining hepatic function.[22] Furthermore, HCC patients with PVTT and HRV are particularly susceptible to hepatic decompensation due to obstruction of the portal vein and progressive alteration of portal pressure.[11–13] A retrospective study has shown the benefits of primary prevention in newly diagnosed HCC patients with HRV, but without focusing on PVTT.[23] Another previous retrospective study highlighted the survival benefits of primary prevention in HCC patients with HRV but did not include a subgroup analysis of patients with PVTT.[4] A more recent study with a limited number of patients with PVTT (25 of 89, 28%) showed the survival benefits of EVL as primary prophylaxis in HCC patients who underwent TACE.[15] Our recent study[16] was the only RCT that investigated the strategy of primary prophylaxis of EVB in HCC patients, and it demonstrated the superiority of EVL over NSBB in patients with early HCC, but these benefits did not extend to advanced HCC. As over 50% of the patients enrolled in this RCT presented with ascites or hepatic

encephalopathy, the strategy of primary prophylaxis for hepatic decompensation in HCC patients with PVTT remains unanswered.

In the current study, we classified 445 patients at initial enrollment as BCLC stage C/D. Two hundred and seventy-three (61.3%) patients with PVTT presented with CSPH, which is higher than the 23~42% seen in patients with early-stage HCC.[4,5] For patients with advanced HCC, most inevitably experienced hepatic decompensation, with 75% of our patients developing variceal bleeding, hepatic encephalopathy, or ascites during the follow-up period. We found that HRV prophylaxis reduced the incidence of EVB and extended the DFS, though it did not improve the OS. Noteworthy is that more patients experienced EVB in the non-prophylaxis group. However, in our subgroup analysis of outcomes between patients with different hepatic decompensation, the EVB group has the shortest DFS but almost the same OS compared to Ascites/HE group, which means most of them can be rescued by EVL and receive the best supportive care, enabling them to survive more than 6 weeks. The incidence of EVB was logically lower in the prophylaxis group, but the overall incidence of hepatic decompensation remains the same, implying that other types of hepatic failure still occurred over time and lead to mortality.

When we examined the effectiveness of NSBB and EVL, we found no difference in DFS or OS between the NSBB and EVL groups. However, the incidence of EVB was higher in the EVL group. In our study, 9 patients (31%) in the EVL group experienced EVB, and 3 (33%) of them encountered EV ulcer bleeding after the first prophylactic EVL within a week. Previous studies have identified PVTT as a risk factor for EVB in HCC patients on primary prophylaxis.[15,23] Furthermore, our previous study demonstrated that PVTT is associated with a higher incidence of recurrent EVB in patients who underwent maintenance EVL.[14] The procedure of EVL causes mechanical injury and EVL ulcers, and the high portal pressure owing to PVTT may increase the risk of EVL ulcer bleeding. Therefore, the primary prophylaxis with EVL in HCC patients with vP4 PVTT should be approached with caution.

We found that IO was associated with improved DFS and OS in our multivariate analysis, which aligns with previous real-world data in patients with CTP class B.[24,25] IO also demonstrated higher tolerability and lower toxicity in patients with decompensated liver function.[25,26] The progression of HCC is associated with severity of portal hypertension,[22] and the better disease control of IO might delay further decompensation.[27] In our subgroup analysis focusing on patients who received IO as first line therapy, the DFS and OS were longer in the prophylaxis group, but the p value was not significant, probably due to limited number of the IO group. Additional feasibility studies were required to investigate the efficacy of prophylaxis in HCC patients with EV under IO.

This study has several limitations. First, the study enrolled HCC patients from 2013 to 2022, a period marked by significant evolution in treatment of advanced HCC. In 2013, the only treatment option was the tyrosine kinase inhibitor Sorafenib. However, by 2022, IO with atezolizumab and bevacizumab, which prolonged survival significantly, had become the recommended first-line treatment.[28] Given this progress in cancer treatment for patients with advanced HCC, we believe the benefits of primary prophylaxis may become significantly manifested, not only the DFS but also the OS. Second, the study's retrospective nature means that the dosage of NSBB and intervals of EVL were not controlled. Although we outlined the starting dose and adjustment protocol for NSBB and EVL, we could not ensure the adherence of every patients, which could potentially diminish the benefits of primary prophylaxis. Third, the diagnosis of PVTT was based either on CT or MRI. However, previous studies suggest a higher reliability for MRI over contrast-enhanced CT in diagnosing bland thrombus or tumor thrombus.[29,30]

Conclusions

In conclusion, this study discovered that primary prophylaxis delays hepatic decompensation yet does not extend OS in HCC patients with PVTT. We found no differences in hepatic decompensation or OS between the NSBB and EVL groups. The first-line IO treatment is independently associated with better DFS and OS. More prospective studies are needed in the IO era to determine if primary prophylaxis can extend OS as patients have a longer lifespan.

Abbreviations

AFP, alpha-fetoprotein; ALBI, albumin-bilirubin; ALK-P, alkaline phosphatase; ALT, alanine aminotransferase; BCLC, the Barcelona Clinic Liver Cancer; CSPH, clinically significant portal hypertension; CTP, Child-Turcotte-Pugh; DFS,

decompensation-free survival; EGD, esophagogastroduodenoscopy; EVB, esophageal variceal bleeding; EVL, endoscopic variceal ligation; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HRV, high-risk varices; HVPG, hepatic venous portal gradient; IO, immunotherapy; MELD, Model For End-Stage Liver Disease; NSBB, nonselective beta-blockers; OS, overall survival; PVTT, portal vein tumor thrombus; PT-INR, prothrombin time international normalized ratio; RCT, randomized controlled trial; RT, radiotherapy; TACE, transarterial chemoembolization; TKI, tyrosine kinase inhibitor.

Data Sharing Statement

Access to the materials and data generated and/or analyzed in this study can be requested from the first author, Yu-Jen Chen.

Ethics Approval and Consent to Participate

The study was carried out in compliance with the Declaration of Helsinki and received approval from the Institutional Review Board of Taipei Veterans General Hospital (VGHIRB No. 2023-11-005CC). Consent waivers were procured for the retrospective study, and patient information along with their records were rendered anonymous and de-identified before being analyzed.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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